CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074843

Trade Name :PROPOXYPHENE NAPSYLATE AND ACETAMINOPHEN TABLETS USP 100MG/650MG

Generic Name: Propoxyphene Napsylate and Acetaminophen Tablets USP 100mg/650mg

Sponsor : Vintage Pharmaceuticals , Inc.

Approval Date: February 12, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074843

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				
Approvable Letter				
Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074843

APPROVAL LETTER

ANDA 74-843

FEB 12 1997

Vintage Pharmaceuticals, Inc.
Attention: Rebecca Thurman
3241 Woodpark Blvd.
Charlotte, NC 28206

Dear Madam:

This is in reference to your abbreviated new drug application dated January 31, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Propoxyphene Napsylate and Acetaminophen Tablets USP, 100 mg/650 mg.

Reference is also made to your amendments dated March 5, May 30, June 5, December 4 and 20, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Propoxyphene Napsylate and Acetaminophen Tablets USP, 100 mg/650 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug Darvocet-N® of Eli Lilly and Co. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

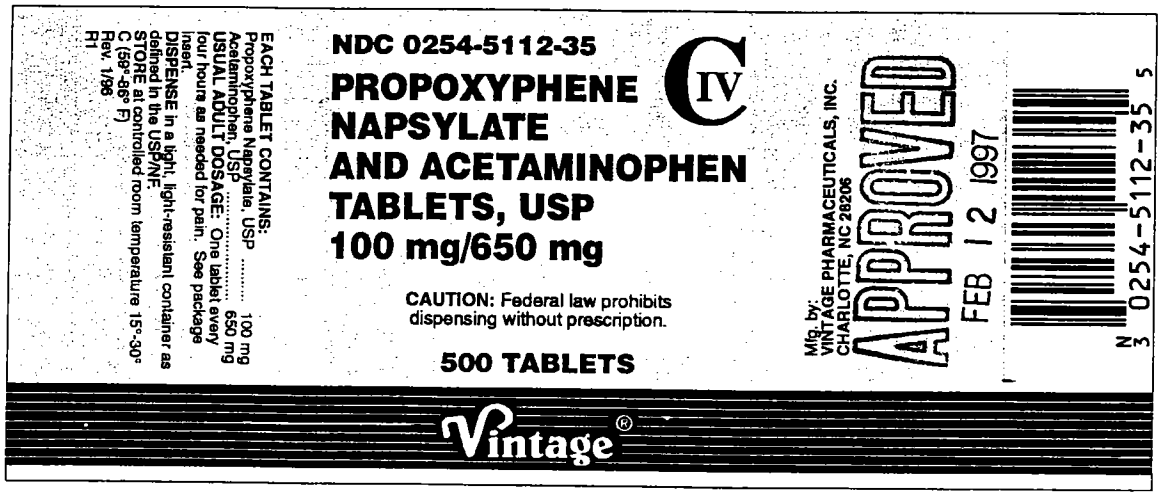
2/12/97

Douglas L. Spoon
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

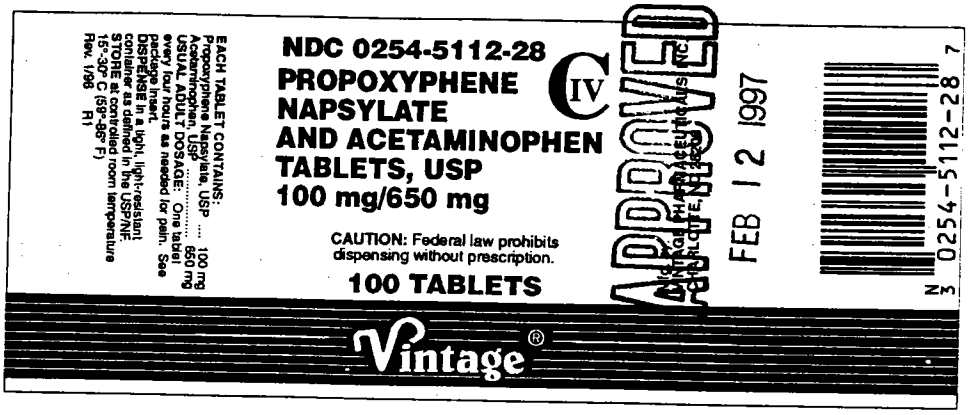
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074843

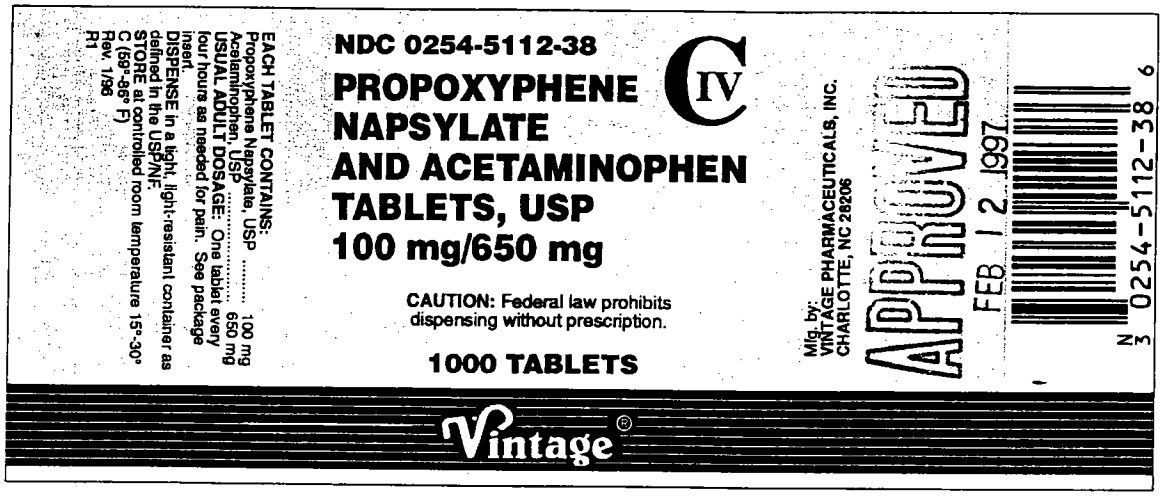
FINAL PRINTED LABELING



LABEL SIZE 2 1/2 X 6 INCHES



LABEL SIZE 2 X 5 INCHES



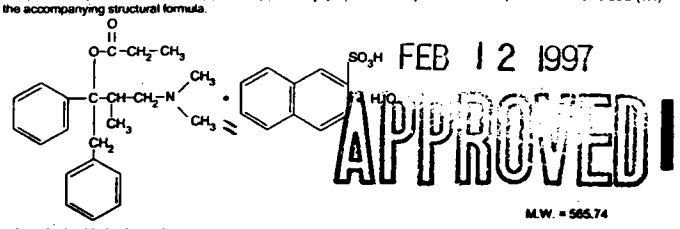
LABEL SIZE 2 1/2 X 6 INCHES

PROPOXYPHENE NAPSYLATE AND ACETAMINOPHEN TABLETS, USP

CIV

DESCRIPTION:

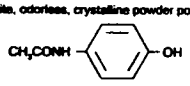
Propoxyphene Napsylate, USP is an odorless, white, crystalline solid with a bitter taste. It is very slightly soluble in water and soluble in methanol, ethanol, chloroform, and acetone. Chemically, it is (αS,1R)-α-[2-(Dimethylamino)-1-methylethyl]-α-phenylphenethyl propionate compound with 2-naphthalenesulfonic acid (1:1) monohydrate, which can be represented by the accompanying structural formula.



$C_{22}H_{29}NO_2 \cdot C_{10}H_8O_3S \cdot H_2O$ M.W. = 565.74

Propoxyphene napsylate differs from propoxyphene hydrochloride in that it allows more stable liquid dosage forms and tablet formulations. Because of differences in molecular weight, a dose of 100 mg (176.8 μmol) of propoxyphene napsylate is required to supply an amount of propoxyphene equivalent to that present in 65 mg (172.9 μmol) of propoxyphene hydrochloride.

The acetaminophen component is 4'-Hydroxyacetanilide, a white, odorless, crystalline powder possessing a slightly bitter taste, and is represented by the following structural formula:



$C_8H_9NO_2$ M.W. = 151.16

Each propoxyphene napsylate and acetaminophen tablet, for oral administration contains 100 mg (176.8 μmol) propoxyphene napsylate and 650 mg (4,300 μmol) acetaminophen.

In addition each tablet contains the following inactive ingredients: D&C Yellow #10 Aluminum Lake, FD&C Red #40 Aluminum Lake, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, polyethylene glycol, polysorbate 80, sodium starch glycolate and titanium dioxide.

CLINICAL PHARMACOLOGY:

Propoxyphene is a centrally acting narcotic analgesic agent. Equimolar doses of propoxyphene hydrochloride or napsylate provide similar plasma concentrations.

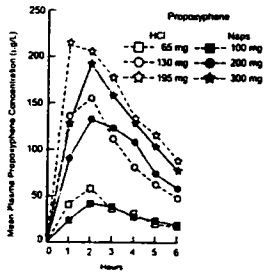


Figure 1. Mean plasma concentrations of propoxyphene in 8 human subjects following oral administration of 65 and 130 mg of the hydrochloride salt and 100 mg and 200 mg of the napsylate salt and in 7 given 195 mg of the hydrochloride and 300 mg of the napsylate salt.

Following administration of 65, 130, or 195 mg of propoxyphene hydrochloride, the bioavailability of propoxyphene is equivalent to that of 100, 200, or 300 mg respectively of propoxyphene napsylate. Peak plasma concentrations of propoxyphene are reached in 2 to 2½ hours. After a 100 mg oral dose of propoxyphene napsylate, peak plasma levels of 0.05 to 0.1 μg/mL are achieved. As shown in Figure 1, the napsylate salt tends to be absorbed more slowly than the hydrochloride. At or near therapeutic doses, this absorption difference is small when compared with that among subjects and among doses.

Because of this several hundredfold difference in solubility, the absorption rate of very large doses of the napsylate salt is significantly lower than that of equimolar doses of the hydrochloride.

Repeated doses of propoxyphene at 6 hour intervals lead to increasing plasma concentrations, with a plateau after the ninth dose at 48 hours.

Propoxyphene is metabolized in the liver to yield norpropoxyphene. Propoxyphene has a half-life of 6 to 12 hours, whereas that of norpropoxyphene is 30 to 36 hours.

Norpropoxyphene has substantially less central nervous system depressant effect than propoxyphene but a greater local anesthetic effect, which is similar to that of amitriptyline and antiarrhythmic agents such as lidocaine and quinidine.

In animal studies in which propoxyphene and norpropoxyphene were continuously infused in large amounts, intracardiac conduction time (PR and QRS intervals) was prolonged. Any intracardiac conduction delay attributable to high concentrations of norpropoxyphene may be of relatively long duration.

Actions:

Propoxyphene is a mild narcotic analgesic structurally related to methadone. The potency of propoxyphene napsylate is from two-thirds to equal that of codeine.

Propoxyphene napsylate and acetaminophen tablets provide the analgesic activity of propoxyphene napsylate and the antipyretic-analgesic activity of acetaminophen.

The combination of propoxyphene and acetaminophen produces greater analgesia than that produced by either propoxyphene or acetaminophen alone.

INDICATIONS AND USAGE:

Propoxyphene napsylate and acetaminophen tablets are indicated for the relief of mild to moderate pain, either when pain is present alone or when it is accompanied by fever.

CONTRAINDICATIONS:

Hypersensitivity to propoxyphene or to acetaminophen.

WARNINGS:

— Do not prescribe propoxyphene for patients who are suicidal or addiction-prone.

— Prescribe propoxyphene with caution for patients taking tranquilizers or antidepressant drugs and patients who use alcohol in excess.

— Tell your patients not to exceed the recommended dose and to limit their intake of alcohol.

Propoxyphene products in excessive doses, either alone or in combination with other CNS depressants, including alcohol, are a major cause of drug-related deaths. Fatalities within the first hour of overdosage are not uncommon. In a survey of deaths due to overdosage conducted in 1975, in approximately 20% of the fatal cases, death occurred within the first hour (5% occurred within 15 minutes). Propoxyphene should not be taken in doses higher than those recommended by the physician. The judicious prescribing of propoxyphene is essential to the safe use of this drug. With patients who are depressed or suicidal, consideration should be given to the use of non-narcotic analgesics. Patients should be cautioned about the concomitant use of propoxyphene products and alcohol because of potentially serious CNS-additive effects of these agents. Because of its added depressant effects, propoxyphene should be prescribed with caution for those patients whose medical condition requires the concomitant administration of sedatives, tranquilizers, muscle relaxants, antidepressants, or other CNS-depressant drugs. Patients should be advised of the additive depressant effects of these combinations.

Many of the propoxyphene-related deaths have occurred in patients with previous histories of emotional disturbances or suicidal ideation or attempts as well as histories of misuse of tranquilizers, alcohol, and other CNS-active drugs. Some deaths have occurred as a consequence of the accidental ingestion of excessive quantities of propoxyphene alone or in combination with other drugs. Patients taking propoxyphene should be warned not to exceed the dosage recommended by the physician.

Drug Dependence

Propoxyphene, when taken in higher-than-recommended doses over long periods of time, can produce drug dependence characterized by psychic dependence and less frequently, physical dependence and tolerance. Propoxyphene will only partially suppress the withdrawal syndrome in individuals physically dependent on morphine or other narcotics. The abuse liability of propoxyphene is qualitatively similar to that of codeine although quantitatively less, and propoxyphene should be prescribed with the same degree of caution appropriate to the use of codeine.

Usage in Ambulatory Patients

Propoxyphene may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.

PRECAUTIONS:

General

Propoxyphene should be administered with caution to patients with hepatic or renal impairment since higher serum concentrations or delayed elimination may occur.

Information for Patients

A Patient Information Sheet is available for this product. See text following "ANIMAL TOXICOLOGY" section below.

Drug Interactions

The CNS-depressant effect of propoxyphene is additive with that of other CNS depressants, including alcohol.

As is the case with many medicinal agents, propoxyphene may slow the metabolism of a concomitantly administered drug. Should this occur, the higher serum concentrations of that drug may result in increased pharmacologic or adverse effects of that drug. Such occurrences have been reported when propoxyphene was administered to patients on antidepressants, anticonvulsants, or warfarin-like drugs. Severe neurologic signs, including coma have occurred with concurrent use of carbamazepine.

Pregnancy

Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Instances of withdrawal symptoms in the neonate have been reported following usage during pregnancy. Therefore, propoxyphene should not be used in pregnant women unless, in the judgement of the physician, the potential benefits outweigh the possible hazards.

Nursing Mothers

Low levels of propoxyphene have been detected in human milk. In postpartum studies involving nursing mothers who were given propoxyphene, no adverse effects were noted in infants receiving mother's milk. Caution should be exercised when propoxyphene napsylate and acetaminophen tablets are administered to a nursing woman.

Pediatric Use

Propoxyphene is not recommended for use in pediatric patients because documented clinical experience has been insufficient to establish safety and a suitable dosage regimen in the pediatric age group.

Usage in the Elderly

The rate of propoxyphene metabolism may be reduced in some patients. Increased dosing interval should be considered.

ADVERSE REACTIONS:

In a survey conducted in hospitalized patients, less than 1% of patients taking propoxyphene hydrochloride at recommended doses experienced side effects. The most frequently reported were dizziness, sedation, nausea, and vomiting. Some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include constipation, abdominal pain, skin rashes, lightheadedness, headache, weakness, euphoria, dysphoria, hallucinations, and minor visual disturbances.

Liver dysfunction has been reported in association with both active components of propoxyphene napsylate and acetaminophen tablets. Propoxyphene therapy has been associated with abnormal liver function tests and, more rarely, with instances of reversible jaundice (including cholestatic jaundice). Hepatic necrosis may result from acute overdose of acetaminophen (see OVERDOSAGE). In chronic ethanol abusers, this has been reported rarely with short-term use of acetaminophen doses of 2.5 to 10 g/day. Fatalities have occurred.

Renal papillary necrosis may result from chronic acetaminophen use, particularly when the dosage is greater than recommended and when combined with aspirin.

Subacute painful myopathy has occurred following chronic propoxyphene overdosage.

OVERDOSAGE

In all cases of suspected overdosage, call your regional Poison Control Center to obtain the most up-to-date information about the treatment of overdose. This

Figure 1. Mean plasma concentrations of propoxyphene in 8 human subjects following oral administration of 65 and 130 mg of the hydrochloride salt and 100 mg and 200 mg of the napsylate salt and in 7 given 195 mg of the hydrochloride and 300 mg of the napsylate salt.

Propoxyphene is a mild narcotic analgesic structurally related to methadone. The potency of propoxyphene napsylate is from two-thirds to equal that of codeine.

Propoxyphene napsylate and acetaminophen tablets provide the analgesic activity of propoxyphene napsylate and the antipyretic-analgesic activity of acetaminophen.

The combination of propoxyphene and acetaminophen produces greater analgesia than that produced by either propoxyphene or acetaminophen alone.

INDICATIONS AND USAGE:

Propoxyphene napsylate and acetaminophen tablets are indicated for the relief of mild to moderate pain, either when pain is present alone or when it is accompanied by fever.

CONTRAINDICATIONS:

Hypersensitivity to propoxyphene or to acetaminophen.

WARNINGS:

— Do not prescribe propoxyphene for patients who are suicidal or addiction-prone.

— Prescribe propoxyphene with caution for patients taking tranquilizers or antidepressant drugs and patients who use alcohol in excess.

— Tell your patients not to exceed the recommended dose and to limit their intake of alcohol.

Propoxyphene products in excessive doses, either alone or in combination with other CNS depressants, including alcohol, are a major cause of drug-related deaths. Fatalities within the first hour of overdosage are not uncommon. In a survey of deaths due to overdosage conducted in 1975, in approximately 20% of the fatal cases, death occurred within the first hour (5% occurred within 15 minutes). Propoxyphene should not be taken in doses higher than those recommended by the physician. The judicious prescribing of propoxyphene is essential to the safe use of this drug. With patients who are depressed or suicidal, consideration should be given to the use of non-narcotic analgesics. Patients should be cautioned about the concomitant use of propoxyphene products and alcohol because of potentially serious CNS-additive effects of these agents. Because of its added depressant effects, propoxyphene should be prescribed with caution for those patients whose medical condition requires the concomitant administration of sedatives, tranquilizers, muscle relaxants, antidepressants, or other CNS-depressant drugs. Patients should be advised of the additive depressant effects of these combinations.

Many of the propoxyphene-related deaths have occurred in patients with previous histories of emotional disturbances or suicidal ideation or attempts as well as histories of misuse of tranquilizers, alcohol, and other CNS-active drugs. Some deaths have occurred as a consequence of the accidental ingestion of excessive quantities of propoxyphene alone or in combination with other drugs. Patients taking propoxyphene should be warned not to exceed the dosage recommended by the physician.

Drug Dependence

Propoxyphene, when taken in higher-than-recommended doses over long periods of time, can produce drug dependence characterized by psychic dependence and less frequently, physical dependence and tolerance. Propoxyphene will only partially suppress the withdrawal syndrome in individuals physically dependent on morphine or other narcotics. The abuse liability of propoxyphene is qualitatively similar to that of codeine although quantitatively less, and propoxyphene should be prescribed with the same degree of caution appropriate to the use of codeine.

Usage in Ambulatory Patients

Propoxyphene may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.

PRECAUTIONS:

General

Propoxyphene should be administered with caution to patients with hepatic or renal impairment since higher serum concentrations or delayed elimination may occur.

Information for Patients

A Patient Information Sheet is available for this product. See text following "ANIMAL TOXICOLOGY" section below.

Drug Interactions

The CNS-depressant effect of propoxyphene is additive with that of other CNS depressants, including alcohol.

As is the case with many medicinal agents, propoxyphene may slow the metabolism of a concomitantly administered drug. Should this occur, the higher serum concentrations of that drug may result in increased pharmacologic or adverse effects of that drug. Such occurrences have been reported when propoxyphene was administered to patients on antidepressants, anticonvulsants, or warfarin-like drugs. Severe neurologic signs, including coma have occurred with concurrent use of carbamazepine.

Pregnancy

Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Instances of withdrawal symptoms in the neonate have been reported following usage during pregnancy. Therefore, propoxyphene should not be used in pregnant women unless, in the judgement of the physician, the potential benefits outweigh the possible hazards.

Nursing Mothers

Low levels of propoxyphene have been detected in human milk. In postpartum studies involving nursing mothers who were given propoxyphene, no adverse effects were noted in infants receiving mother's milk. Caution should be exercised when propoxyphene napsylate and acetaminophen tablets are administered to a nursing woman.

Pediatric Use

Propoxyphene is not recommended for use in pediatric patients because documented clinical experience has been insufficient to establish safety and a suitable dosage regimen in the pediatric age group.

Usage in the Elderly

The rate of propoxyphene metabolism may be reduced in some patients. Increased dosing interval should be considered.

ADVERSE REACTIONS:

In a survey conducted in hospitalized patients, less than 1% of patients taking propoxyphene hydrochloride at recommended doses experienced side effects. The most frequently reported were dizziness, sedation, nausea, and vomiting. Some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include constipation, abdominal pain, skin rashes, lightheadedness, headache, weakness, euphoria, dysphoria, hallucinations, and minor visual disturbances.

Liver dysfunction has been reported in association with both active components of propoxyphene napsylate and acetaminophen tablets. Propoxyphene therapy has been associated with abnormal liver function tests and, more rarely, with instances of reversible jaundice (including cholestatic jaundice). Hepatic necrosis may result from acute overdose of acetaminophen (see OVERDOSAGE). In chronic ethanol abusers, this has been reported rarely with short-term use of acetaminophen doses of 2.5 to 10 g/day. Fatalities have occurred.

Renal papillary necrosis may result from chronic acetaminophen use, particularly when the dosage is greater than recommended and when combined with aspirin.

Subacute painful myopathy has occurred following chronic propoxyphene overdosage.

OVERDOSAGE

In all cases of suspected overdosage, call your regional Poison Control Center to obtain the most up-to-date information about the treatment of overdose. This recommendation is made because, in general, information regarding the treatment of overdosage may change more rapidly than do package inserts.

Initial consideration should be given to the management of the CNS effects of propoxyphene overdosage. Resuscitative measures should be initiated promptly.

Symptoms of Propoxyphene Overdosage

The manifestations of acute overdosage with propoxyphene are those of narcotic overdosage. The patient is usually somnolent but may be stuporous or comatose and convulsing. Respiratory depression is characteristic. The ventilatory rate and/or tidal volume is decreased, which results in cyanosis and hypoxia. Pupils, initially pinpoint, may become dilated as hypoxia increases. Cheyne-Stokes respiration and apnea may occur. Blood pressure and heart rate are usually normal initially, but blood pressure falls and cardiac performance deteriorates, which ultimately results in pulmonary edema and circulatory collapse, unless the respiratory depression is corrected and adequate ventilation is restored promptly. Cardiac arrhythmias and conduction delay may be present. A combined respiratory-metabolic acidosis occurs owing to retained CO_2 (hypercapnia) and to lactic acid formed during anaerobic glycolysis. Acidosis may be severe if large amounts of salicylates have also been ingested. Death may occur.

Treatment of Propoxyphene Overdosage

Attention should be directed first to establishing a patent airway and to restoring ventilation. Mechanically assisted ventilation, with or without oxygen, may be

required, and positive pressure respiration may be desirable if pulmonary edema is present. The narcotic antagonist naloxone will markedly reduce the degree of respiratory depression, and 0.4 to 2 mg should be administered promptly, preferably intravenously. If the desired degree of counteraction with improvement in respiratory functions is not obtained, naloxone should be repeated at 2 to 3 minute intervals. The duration of action of the antagonist may be brief. If no response is observed after 10 mg of naloxone have been administered, the diagnosis of propoxyphene toxicity should be questioned. Naloxone may also be administered by continuous intravenous infusion.

Treatment of Propoxyphene Overdosage in Children

The usual initial dose of naloxone in children is 0.01 mg/kg body weight given intravenously. If this dose does not result in the desired degree of clinical improvement, a subsequent increased dose of 0.1 mg/kg body weight may be administered. If an IV route of administration is not available, naloxone may be administered IM or subcutaneously in divided doses. If necessary, naloxone can be diluted with Sterile Water for Injection.

Blood gases, pH, and electrolytes should be monitored in order that acidosis and any electrolyte disturbance present may be corrected promptly. Acidosis, hypoxia, and generalized CNS depression predispose to the development of cardiac arrhythmias. Ventricular fibrillation or cardiac arrest may occur and necessitate the full complement of cardiopulmonary resuscitation (CPR) measures. Respiratory acidosis rapidly subsides as ventilation is restored and hypercapnea eliminated, but lactic acidosis may require intravenous bicarbonate for prompt correction.

Electrocardiographic monitoring is essential. Prompt correction of hypoxia, acidosis, and electrolyte disturbance (when present) will help prevent these cardiac complications and will increase the effectiveness of agents administered to restore normal cardiac function.

In addition to the use of a narcotic antagonist, the patient may require careful titration with an anticonvulsant to control convulsions. Analeptic drugs (for example, caffeine or amphetamine) should not be used because of their tendency to precipitate convulsions.

General supportive measures, in addition to oxygen, include, when necessary, intravenous fluids, vasopressor-inotropic compounds, and when infection is likely, anti-infective agents. Gastric lavage may be useful, and activated charcoal can adsorb a significant amount of ingested propoxyphene. Dialysis is of little value in poisoning due to propoxyphene. Efforts should be made to determine whether other agents, such as alcohol, barbiturates, tranquilizers or other CNS depressants, were also ingested, since these increase CNS depression as well as cause specific toxic effects.

Symptoms of Acetaminophen Overdosage:

Shortly after oral ingestion of an overdosage of acetaminophen and for the next 24 hours, anorexia, nausea, vomiting, diaphoresis, general malaise, and abdominal pain have been noted. The patient may then present no symptoms, but evidence of liver dysfunction may become apparent up to 72 hours after ingestion, with elevated serum transaminase and lactic dehydrogenase levels, an increase in serum bilirubin concentrations, and a prolonged prothrombin time. Death from hepatic failure may result 3 to 7 days after overdosage.

Acute renal failure may accompany the hepatic dysfunction and has been noted in patients who do not exhibit signs of fulminant hepatic failure. Typically, renal impairment is more apparent 6 to 9 days after ingestion of the overdose.

Treatment of Acetaminophen Overdosage:

Acetaminophen in massive overdosage may cause hepatic toxicity in some patients. ***In all cases of suspected overdose, immediately call your regional poison center or Rocky Mountain Poison Control Center's toll-free number (800-525-6115)*** for assistance in diagnosis and for directions in the use of N-acetylcysteine as an antidote.

In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 g and fatalities with less than 15 g. Importantly, young children seem to be more resistant than adults to the hepatotoxic effect of an acetaminophen overdose. Despite this, the measures outlined below should be initiated in any adult or child suspected of having ingested an acetaminophen overdose.

Because clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours postingestion, liver function studies should be obtained initially and repeated at 24 hour intervals.

Consider emptying the stomach promptly by lavage or by induction of emesis with syrup of ipecac. Patients' estimates of the quantity of a drug ingested are notoriously unreliable. Therefore, if an acetaminophen overdose is suspected, a serum acetaminophen assay should be obtained as early as possible, but no sooner than 4 hours following ingestion. The antidote, N-acetylcysteine, should be administered as early as possible, preferably within 16 hours of the overdose ingestion for optimal results. Following recovery, there are no residual, structural, or functional hepatic abnormalities.

DOSAGE AND ADMINISTRATION:

This product is given orally. The usual dose is 100 mg propoxyphene napsylate and 650 mg acetaminophen every 4 hours as needed for pain. The maximum recommended dose of propoxyphene napsylate is 600 mg per day.

Consideration should be given to a reduced total daily dosage in patients with hepatic or renal impairment.

HOW SUPPLIED

Propoxyphene napsylate and acetaminophen tablets contain 100 mg propoxyphene napsylate and 650 mg acetaminophen. They are supplied as red film coated, unscored, capsule shaped tablets, debossed "5112" and "V" in containers of 100, 500 and 1000 tablets. Dispense in a tight, light resistant container as defined in the USP/NF with a child-resistant closure.

Storage: Store at controlled room temperature, 15° - 30°C (59° - 86° F).

Caution: Federal law prohibits dispensing without prescription.

ANIMAL TOXICOLOGY

The acute lethal doses of the hydrochloride and napsylate salts of propoxyphene were determined in 4 species. The results shown in Figure 2 indicate that on a molar basis, the napsylate salt is less toxic than the hydrochloride. This may be due to the relative insolubility and retarded absorption of propoxyphene napsylate.

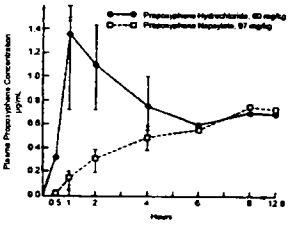
FIGURE 2

ACUTE ORAL TOXICITY OF PROPOXYPHENE

$\frac{LD_{50}\ (mg/kg) \pm SE}{LD_{50}\ (mmol/kg)}$

Species	Propoxyphene Hydrochloride	Propoxyphene Napsylate
Mouse	282 ± 39 / 0.75	915 ± 163 / 1.62
Rat	230 ± 44 / 0.61	647 ± 95 / 1.14
Rabbit	ca 82 / 0.22	>183 / >0.32
Dog	ca 100 / 0.27	>183 / >0.32

Figure 3



Some indication of the relative insolubility and retarded absorption of propoxyphene napsylate was obtained by measuring plasma propoxyphene levels in 2 groups of 4 dogs following oral administration of equimolar doses of the 2 salts.

As shown in Figure 3, the peak plasma concentration observed with propoxyphene hydrochloride was much higher than that obtained after administration of the napsylate salt.

Although none of the animals in this experiment died, 3 of the 4 dogs given propoxyphene hydrochloride exhibited convulsive seizures during the time interval corresponding to the peak plasma levels. The 4 animals receiving the napsylate salt were ataxic but not acutely ill.

Figure 3. Plasma proxyphene concentrations in dogs following large doses of the hydrochloride and napsylate salts.

The following information includes the maximum daily dosage and is available to patients receiving propoxyphene napsylate and acetaminophen tablets.

Patient Information Sheet

YOUR PRESCRIPTION FOR A PROPOXYPHENE PRODUCT

SUMMARY

Products containing Propoxyphene are used to relieve pain.

LIMIT YOUR INTAKE OF ALCOHOL WHILE TAKING THIS DRUG. Make sure your doctor knows if you are taking tranquilizers, sleep aids, antidepressants, antihistamines, or any other drugs that make you sleepy. Combining propoxyphene with alcohol or these drugs in excessive doses is dangerous.

Use care while driving a car or using machines until you see how the drug affects you because propoxyphene can make you sleepy. Do not take more of the drug than your doctor prescribed. Dependence has occurred when patients have taken propoxyphene for a long period of time at doses greater than recommended.

The rest of this leaflet gives you more information about propoxyphene. Please read it and keep it for future use.

Uses for Propoxyphene

Products containing propoxyphene are used for the relief of mild to moderate pain. Products that contain propoxyphene plus acetaminophen are prescribed for the relief of pain or pain associated with fever.

Before Taking Propoxyphene

Make sure your doctor knows if you have ever had an allergic reaction to propoxyphene or acetaminophen.

The effect of propoxyphene in children under 12 has not been studied, therefore, use of the drug in this age group is not recommended.

How to Take Propoxyphene

Follow your doctor's directions exactly. Do not increase the amount you take without your doctor's approval. If you miss a dose of the drug, do not take twice as much the next time.

Pregnancy

Do not take propoxyphene during pregnancy unless your doctor knows you are pregnant and specifically recommends its use. Cases of temporary dependence in the newborn have occurred when the mother has taken propoxyphene consistently in the weeks before delivery. As a general principle, no drug should be taken during pregnancy unless it is clearly necessary.

General Cautions

Heavy use of alcohol with propoxyphene is hazardous and may lead to overdosage symptoms (see "Overdose" below). THEREFORE, LIMIT YOUR INTAKE OF ALCOHOL WHILE TAKING PROPOXYPHENE.

Combinations of excessive doses of propoxyphene, alcohol, and tranquilizers are dangerous. Make sure your doctor knows if you are taking tranquilizers, sleep aids, antidepressant drugs, antihistamines, or any other drugs that make you sleepy. The use of these drugs with propoxyphene increases their sedative effects and may lead to overdosage symptoms, including death (see "Overdose" below)

Propoxyphene may cause drowsiness or impair your mental and/or physical abilities; therefore, use caution when driving a vehicle or operating dangerous machinery. DO NOT perform any hazardous task until you have seen your response to this drug.

Propoxyphene may increase the concentration in the body of medications such as anticoagulants ("blood thinners"), antidepressants, or drugs used for epilepsy. The result may be excessive or adverse effects of these medications. Make sure your doctor knows if you are taking any of these medications.

Dependence

You can become dependent on propoxyphene if you take it in higher than recommended doses over a long period of time. Dependence is a feeling of need for the drug and a feeling that you cannot perform normally without it.

Overdose

An overdose of propoxyphene alone or in combination with other drugs, including alcohol, may cause weakness, difficulty in breathing, confusion, anxiety, and more severe drowsiness and dizziness. Extreme overdosage may lead to unconsciousness and death.

This product contains acetaminophen. Acetaminophen overdosage symptoms include nausea, vomiting, lack of appetite, and abdominal pain. Liver damage may occur even after symptoms disappear. Death can occur days later.

In any suspected overdosage situation, contact your doctor or nearest hospital emergency room. GET EMERGENCY HELP IMMEDIATELY.

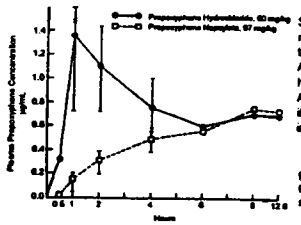
KEEP THIS DRUG AND ALL DRUGS OUT OF THE REACH OF CHILDREN

Possible Side Effects

When propoxyphene is taken as directed, side effects are infrequent. Among those reported are drowsiness, dizziness, nausea, and vomiting. If these effects occur,

Species	LD_{50} (mg/kg) ± SE LD_{50} (mmol/kg) Propoxyphene Hydrochloride	Propoxyphene Napsylate
Mouse	282 ± 39 0.75	915 ± 163 1.62
Rat	230 ± 44 0.61	647 ± 95 1.14
Rabbit	ca 82 0.22	>183 >0.32
Dog	ca 100 0.27	>183 >0.32

Figure 3



Some indication of the relative insolubility and retarded absorption of propoxyphene napsylate was obtained by measuring plasma propoxyphene levels in 2 groups of 4 dogs following oral administration of equimolar doses of the 2 salts.

As shown in Figure 3, the peak plasma concentration observed with propoxyphene hydrochloride was much higher than that obtained after administration of the napsylate salt.

Although none of the animals in this experiment died, 3 of the 4 dogs given propoxyphene hydrochloride exhibited convulsive seizures during the time interval corresponding to the peak plasma levels. The 4 animals receiving the napsylate salt were ataxic but not acutely ill.

Figure 3. Plasma propxyphene concentrations in dogs following large doses of the hydrochloride and napsylate salts.

The following information includes the maximum daily dosage and is available to patients receiving propoxyphene napsylate and acetaminophen tablets.

Patient Information Sheet

YOUR PRESCRIPTION FOR A PROPOXYPHENE PRODUCT

SUMMARY

Products containing Propoxyphene are used to relieve pain.

LIMIT YOUR INTAKE OF ALCOHOL WHILE TAKING THIS DRUG. Make sure your doctor knows if you are taking tranquilizers, sleep aids, antidepressants, antihistamines, or any other drugs that make you sleepy. Combining propoxyphene with alcohol or these drugs in excessive doses is dangerous.

Use care while driving a car or using machines until you see how the drug affects you because propoxyphene can make you sleepy. Do not take more of the drug than your doctor prescribed. Dependence has occurred when patients have taken propoxyphene for a long period of time at doses greater than recommended.

The rest of this leaflet gives you more information about propoxyphene. Please read it and keep it for future use.

Uses for Propoxyphene

Products containing propoxyphene are used for the relief of mild to moderate pain. Products that contain propoxyphene plus acetaminophen are prescribed for the relief of pain or pain associated with fever.

Before Taking Propoxyphene

Make sure your doctor knows if you have ever had an allergic reaction to propoxyphene or acetaminophen.

The effect of propoxyphene in children under 12 has not been studied, therefore, use of the drug in this age group is not recommended.

How to Take Propoxyphene

Follow your doctor's directions exactly. Do not increase the amount you take without your doctor's approval. If you miss a dose of the drug, do not take twice as much the next time.

Pregnancy

Do not take propoxyphene during pregnancy unless your doctor knows you are pregnant and specifically recommends its use. Cases of temporary dependence in the newborn have occurred when the mother has taken propoxyphene consistently in the weeks before delivery. As a general principle, no drug should be taken during pregnancy unless it is clearly necessary.

General Cautions

Heavy use of alcohol with propoxyphene is hazardous and may lead to overdosage symptoms (see "Overdose" below). THEREFORE, LIMIT YOUR INTAKE OF ALCOHOL WHILE TAKING PROPOXYPHENE.

Combinations of excessive doses of propoxyphene, alcohol, and tranquilizers are dangerous. Make sure your doctor knows if you are taking tranquilizers, sleep aids, antidepressant drugs, antihistamines, or any other drugs that make you sleepy. The use of these drugs with propoxyphene increases their sedative effects and may lead to overdosage symptoms, including death (see "Overdose" below).

Propoxyphene may cause drowsiness or impair your mental and/or physical abilities; therefore, use caution when driving a vehicle or operating dangerous machinery. DO NOT perform any hazardous task until you have seen your response to this drug.

Propoxyphene may increase the concentration in the body of medications such as anticoagulants ("blood thinners"), antidepressants, or drugs used for epilepsy. The result may be excessive or adverse effects of these medications. Make sure your doctor knows if you are taking any of these medications.

Dependence

You can become dependent on propoxyphene if you take it in higher than recommended doses over a long period of time. Dependence is a feeling of need for the drug and a feeling that you cannot perform normally without it.

Overdose

An overdose of propoxyphene alone or in combination with other drugs, including alcohol, may cause weakness, difficulty in breathing, confusion, anxiety, and more severe drowsiness and dizziness. Extreme overdosage may lead to unconsciousness and death.

This product contains acetaminophen. Acetaminophen overdosage symptoms include nausea, vomiting, lack of appetite, and abdominal pain. Liver damage may occur even after symptoms disappear. Death can occur days later.

In any suspected overdosage situation, contact your doctor or nearest hospital emergency room. GET EMERGENCY HELP IMMEDIATELY.

KEEP THIS DRUG AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Possible Side Effects

When propoxyphene is taken as directed, side effects are infrequent. Among those reported are drowsiness, dizziness, nausea, and vomiting. If these effects occur, it may help if you lie down and rest.

Less frequently reported side effects are constipation, abdominal pain, skin rashes, lightheadedness, headache, weakness, hallucinations, minor visual disturbances, and feelings of elation or discomfort.

If side effects occur and concern you, contact your doctor.

Other Information

The safe and effective use of propoxyphene depends on your taking it exactly as directed. This drug has been prescribed specifically for you and your present condition. Do not give this drug to others who may have similar symptoms. Do not use it for any other reason.

If you would like more information about propoxyphene, ask your doctor or pharmacist. They have a more technical leaflet (professional labeling) you may read.

Manufactured by:
Vintage Pharmaceuticals, Inc.
Charlotte, NC 28206

IN-122
12/96
R3

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074843

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO: 3

2. ANDA # 74-843

3. NAME AND ADDRESS OF APPLICANT
Vintage Pharmaceuticals, Inc.
Attention: Rebecca A. Thurman
3241 Woodpark Blvd.
Charlotte, NC 28206

4. LEGAL BASIS FOR SUBMISSION
Generic version of Eli Lilly's Darvocet-N 100. Under Section 505 (j)(2)(A)(vii) of the Federal Food, Drug and Cosmetic Act, this listed drug is not covered by any patent or marketing exclusivity.

6. PROPRIETARY NAME
Darvocet-N 100

7. NONPROPRIETARY NAME
Propoxyphene Napsylate and Acetaminophen Tablets, USP

8. SUPPLEMENTS PROVIDED FOR
N/A

9. AMENDMENTS AND OTHER DATES
January 31, 1996-- Original Submission
March 5, 1996-- Original Correspondence (re:bioequivalence)
May 30, 1996-- Original Correspondence (re:bioequivalence)
June 5, 1996-- Original Correspondence (re:bioequivalence)
June 19, 1996-- FDA requested major amendment (Chemistry/labeling deficiencies)
July 16, 1996-- Bioequivalence study accepted; FDA communication to the firm
July 24, 1996-- Response to deficiencies (chemistry & labeling) by firm
November 27, 1996 -- FDA requested minor amendment (Chemistry/labeling deficiencies)
December 4, 1996 -- Response to deficiencies (Chem & Labeling) by the firm
December 20, 1996 -- Final Printed Labeling submitted by firm

10. PHARMACOLOGICAL CATEGORY
Analgesic/antipyretic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(S)

ary

13. DOSAGE FORM
Oral Tablets

14. POTENCY
100 mg/650 mg

15. CHEMICAL NAME AND STRUCTURE

Propoxyphene Napsylate: α(+)-4-(Dimethylamino)-3-methyl-1,2-diphenyl-2-butanol propionate 2-naphathalene sulfonate hydrate and acetaminophen.

16. RECORDS AND REPORTS
N/A

17. COMMENT
All deficiencies are corrected.

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend approval letter to issue.

19. REVIEWER:

Radhika Rajagopalan, Ph.D.

DATE COMPLETED:

December 17, 1996

12/17/96

1/9/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074843

BIOEQUIVALENCE REVIEWS

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74-843 SPONSOR : Vintage

DRUG & DOSAGE FORM : Propoxyphene Napsylate/Acetaminophen Tablet

STRENGTH (s) : 100 mg/650 mg

TYPE OF STUDY: (SD) Fast SDF MULT OTHER

STUDY SITE: CLINICAL : ANALYTICAL :

STUDY SUMMARY :

Parameter	test PN*	test AA*	ref PN	ref AA	ratio PN	ratio AA	90% CI (log). PN	N	AA	N
Cmax(ng/ml)	67.90	7.43	68.31	7.77	0.99	1.02	87-111	31	92-109	31
AUC(0-T) ngxhr/ml	363	28.23	383.0	27.65	0.95	1.02	83-110	31	99-105	31
AUC(0-Inf) ngxhr/ml	395.1 **406.7	29.30	445.6 **421.5	28.11	0.89 **0.95	1.04	79-106 **87-109	22 21	100-107	22
Tmax hr	2.08	0.96	2.20	0.78	0.95	0.98				
Half-life hr	6.17 **6.36	4.07	6.38 **6.10	3.80	0.97 **1.04	1.07				

See Attachment

* PN = Propoxyphene Napsylate * AA = Acetaminophen ** Without subject 8

DISSOLUTION :

Conditions

Time(min)	Test Mean(range) Acetaminophen	Test Mean(range) Propoxyphene Nap	Ref. Mean(range) Acetaminophen	Ref. Mean(range) Propoxyphen Nap
~~15~~				
~~30~~ 10	83	62	59	36
~~45~~ 20	102	88	95	74
30	103	97	101	89
~~Q =~~ 45	106	99	102	95
60	106	101	101	96

Q = 60 min both

PRIMARY REVIEWER : BRANCH : I

INITIAL : _____ DATE : 1/23/97

BRANCH CHIEF : BRANCH : I

INITIAL : _____ DATE : 1/23/97

Acting

DIRECTOR
DIVISION OF BIOEQUIVALENCE

INITIAL : _____ DATE : 2/7/97

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL : _____ DATE : _____

ANDA 74-843

Vintage Pharmaceuticals, Inc.
Attention: Rebecca A. Thurman
3241 Woodpark Blvd.
Charlotte NC 28206

JUL 16 1996

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Propoxyphene Napsylate and Acetaminophen Tablets USP, 100 mg/650 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 500 mL of pH 4.5 acetate buffer, at 37°C using USP 23 apparatus I (basket) at 100 rpm. The test product should meet the following specifications:

   > Not less than of the labeled amount of both propoxyphene napsylate and acetaminophen in the dosage form are dissolved in 60 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JUL 10 1996

Propoxyphene Napsylate/	Vintage Pharmaceuticals, Inc.
Acetaminophen	Charlotte, North Carolina
Tablet, 100 mg/ 650 mg	Submission Date:
ANDA #74-843	January 31, 1996
Reviewer: James Chaney	March 5, 1996
WP#74843s.196	May 30, 1996
	June 5, 1996

Review of a Bioequivalence Study and Dissolution Data

I. Chronology of Submissions

1/31/96	The original ANDA was submitted. However, the stability data on propoxyphene napsylate and acetaminophen in frozen plasma was included only for the first few days of storage in frozen plasma which was far short of the time that the samples were actually stored before analysis.
3/5/96	The firm submitted the remainder of the quantitative stability data on propoxyphene napsylate and acetaminophen in frozen plasma establishing stability over the period of time corresponding to the time and temperature at which the frozen plasma samples were actually stored in the bioequivalence study. However the reviewer was not aware of this amendment.
5/22/96	The firm was called and requested to send the pharmacokinetic data on disks.
5/30/96	The firm submitted the requested pharmacokinetic data on duplicate disks.
6/5/96	The firm submitted partial text of the bioequivalency studies on duplicate disks. A mere (inadequate) qualitative statement was submitted on this bioequivalence text diskette saying propoxyphene napsylate and acetaminophen in frozen plasma were stable up to 111 and 112 days, respectivelly.
7/5/96	The firm was advised by phone that complete quantitative stability data on propoxyphene napsylate and acetaminophen in frozen plasma should be submitted in writing covering the period of time corresponding to the time and temperature at which the frozen plasma samples were actually stored in the bioequivalence study.
7/8/96	The reviewer was made aware that the desired amendment had been submitted on 3/5/96. The amendment was determined to be satisfactory.

II. Biostudy Objective

The purpose of this study was to compare the relative bioavailability of Vintage propoxyphene napsylate and acetaminophen tablets, 100/650 mg, with that of Darvocet-N^{R} 100 tablets when given after an overnight fast to healthy, adult, male subjects.

III. Background

Propoxyphene is a centrally acting narcotic analgesic agent. The combination of propoxyphene and acetaminophen produces greater analgesia than that produced by either propoxyphene or acetaminophen alone.

Peak plasma concentrations of propoxyphene after oral administration of propoxyphene napsylate are reached in about 2 hours. Its napsylate salt tends to be absorbed more slowly than the hydrochloride. It is metabolized in liver and has a half-life of 6 to 12 hours. Acetaminophen is rapidly and completely absorbed from the gastrointestinal tract with peak plasma levels occurring at about 0.5-1.0 hour post dose. The elimination half-life is approximately 3 hours.

IV. Investigator and Facilities

.. was the Principal Investigator and was responsible for the conduct of this study.

were sub-investigators for this study. Samples for pharmacokinetics analysis were assayed by the analytical laboratory of All subjects were housed and fed at the clinical facility of

Samples for clinical safety analysis (drug screening, chemistry, hematology and urinalysis) were analyzed by with facilities in

V. Clinical Procedures

Criteria for Inclusion/Exclusion of Patients

The 32 subjects who participated in this study were normal, healthy males, in the age range of 19-50 years, and within 15% of their ideal weight as specified in the protocol. All subjects were selected based on the absence of any clinically significant findings on the medical history, physical examination, and clinical laboratory evaluations. Findings which were outside ±10% of the normal range were evaluated individually by the Investigator. All were determined to be not clinically significant for those subjects enrolled in the study.

Formulations

Test (A)	100 mg propoxyphene napsylate with 650 mg acetaminophen tablets, Vintage Pharmaceuticals, Inc. Lot #031045, Exp. date 3/97.
Reference (B)	Darvocet-N^{R} 100 tablets (containing 100 mg propoxyphene napsylate and 650 mg acetaminophen) Eli Lilly & Co. Lot #9AC14A; Exp. Date 2/98.

Dose Administration

The subjects received the test and reference after an overnight fast. The order of treatments was according to the randomization schedule. All doses were administered at a rate of 2 subjects per minute with 240 ml of room temperature water following a 10-hour fast. A thorough mouth check was performed to ensure that the tablet was swallowed. All subjects remained under observation sitting upright or standing for 4 hours after each dosing. Thirty-two (32) subjects were dosed in Period I and 31 were dosed in Period II.

Blood Sampling

In each period, blood samples were collected prior to dosing and at the following nominal times after dosing: 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24 and 30 hours. All plasma samples were stored frozen at -20°C (±5°) until transfer to the laboratory for analysis.

Restrictions

Prior to check-in for the study, the subjects were instructed to take no prescribed medications for at least 14 days prior to the initial dosing and throughout the study. No over-the-counter medications were permitted for 72 hours before dosing in each study period. No medications were permitted during confinement except those administered. Subjects were also instructed to abstain from any products containing alcohol or caffeine for 48 hours prior to dosing and throughout each confinement. None of the subjects reported taking any restricted substance within the time frames indicated.

During the confinement periods of the study, water was restricted one hour before and after dosing except for water (240 ml) administered with the dose. Water was permitted ad lib at all other times. Subjects remained sitting upright or standing for 4 hours after each dosing, except as required for study procedures. No strenuous physical exercise was permitted during confinement. Smoking was restricted for 30 minutes before each vital sign.

Safety

Blood pressure (sitting) and pulse rate were measured before each dosing. The Investigator considered the measurements of all subjects as clinically acceptable for dosing. Blood pressure and pulse rate measurements (sitting) were obtained approximately 2 hours after each dose (within ±15 minutes) and prior to release in each period to monitor the health of the subjects.

Additional Study Information

approved this study prior to its commencement. All of the subjects signified their willingness to participate in this study by signing the approved consent form; a copy was provided to each subject.

In each period, all subjects reported for check-in (Day -1) at least 12 hours before dosing. Meals were provided on check-in day and completed at least 10 hours prior to scheduled dosing time. No food or beverages (except water) were permitted after 10 PM. The same menu was used during each study period. A 7-day washout separated the dosings.

A dosing randomization schedule using 2 sequences was generated by study commencement.

VI. Analytical Procedures - Propoxyphene

Pre-Study Assay Validation

VIII. Pharmacokinetic Data

All the available data from the 31 subjects with reported propoxyphene and acetaminophen concentrations were used in the pharmacokinetic analyses. Pharmacokinetic parameters (areas, times to peak, and elimination rates and half-lives) were calculated using the actual rather than the scheduled times of sample collection. Any sample with a missing value was treated as if the sample had not been scheduled for collection.

IX. Statistical Analysis

Statistical analyses were performed using the General Linear Models (GLM) procedure of the SAS statistical program. Hypothesis testing for treatment effects was conducted at $\alpha = 0.05$. The statistical model contained main effects of sequence, subject within sequence, period, and treatment. Sequence effects were tested against the type III mean square term for subjects within sequence. All other main effects were tested against the mean square error term. The observed and calculated pharmacokinetic parameters as well as the propoxyphene and acetaminophen concentrations at each of the individual collection times were compared statistically. Power for the pair-wise pharmacokinetic comparisons was calculated as the

probability ($\alpha = 0.05$) of detecting a difference equal to 20% of the mean for the reference treatment in the comparison. Confidence Intervals (90%) for pair-wise area and peak concentration comparisons were calculated by the t-test approach (2,1-sided) at $\alpha = 0.10$ overall, $\alpha = 0.05$ each side. The intervals were computed for the "true" mean treatment differences, expressed as a percent of the reference treatment mean, and true geometric mean ratios (from logarithmic transformation).

X. Results

A total of 32 subjects were entered into the study and 31 subjects completed the study. Subject 32 voluntarily withdrew from the study after the 16 hour blood sample in Period I (10/25/95).

All subjects who entered the study met the inclusion/exclusion criteria specified in the protocol with one exception. Subject 03 received an investigational drug in a previous study approximately 24 days prior to screening. In addition, more than 200 ml of blood may have been lost by this subject during this previous study. A post-study audit by disclosed this deviation after completion of this study. Completed case report forms were reviewed and signed by the investigator.

When the propoxyphene elimination data were examined, it was apparent that the difference in elimination halflives for Subject 08 between Periods I (after the reference) and Period II (after the test) was dramatically different (halflives were 13.8 and 3.9 hours, respectively). No other subject demonstrated such a difference between study periods. The elimination phase for Subject 08 may not have been adequately characterized for Period II because the concentration of propoxyphene after 12 hours fell below the level of sensitivity for the assay.

Table 1.1 summarizes the results of the propoxyphene statistical analyses of the major bioavailability parameters excluding Subject 08 from the area-to-infinity and elimination parameters. For completeness, area-to-infinity and elimination parameters were also calculated including the data from Subject 08 (Table 1.3). Log-transformation of the area and Cmax parameters was also performed and analyzed statistically (Tables 1.2 and 1.4).

The plasma concentration-time mean profiles (N=31) for the test and reference products are similar to each other (Table 1.5 and Figure 1).

Table 1.1. Comparisons of propoxyphene results for Vintage's 100 mg propoxyphene napsylate and 650 mg acetaminophen combination tablets (Test) vs. Darvocet-N^R 100 tablets (Reference) when given as a single fasted dose to 31 subjects. AUCinf, Ke and Elimhalf (indicated with *) were determined without data from subject 08.

Parameter	Least Squares Means		Observed Difference (%) [1]	Power	90% Confidence Interval [2]	
	Test	Reference			Lower (%)	Upper (%)
AUC 0-t (ng-hr/ml)	363.9	383.0	-5.01	0.61	-19.6	9.6
AUCinf * (ng-hr/ml)	406.7	421.5	-3.51	0.94	-12.8	5.7
Cmax (ng/ml)	67.90	68.31	-0.60	0.78	-12.7	11.5
Tmax (hour)	2.08	2.20	-5.52	0.98	-	-
Ke * (1/hour)	0.1575	0.1624	-3.07	0.83	-	-
Elimhalf * (hour)	6.36	6.10	4.22	0.98	-	-

[1] Observed difference calculated as: [(Test - Reference) / Reference] x 100. None of the differences were detected as statistically significant by ANOVA ($\alpha = 0.05$). [2] Confidence interval on the observed difference.
* Excluding data from Subject 08.

Table 1.2 Ln-transformation of the propoxyphene pharmacokinetic data.

Parameter	Geometric Mean Ratio: Test/Reference	90% Confidence Interval on Ratio	
		Lower	Upper
AUC 0-t	0.955	0.830	1.098
AUCinf *	0.974	0.874	1.086
Cmax	0.983	0.873	1.107

* Excluding data from Subject 08.

Table 1.3. Comparisons of propoxyphene results for Vintage's 100 mg propoxyphene napsylate and 650 mg acetaminophen combination tablets (Test) vs. Darvocet-N^{R} 100 tablets (Reference) when given as a single fasted dose to 31 subjects. (AUCinf. Ke and Elimhalf were determined including the data from Subject 08.)

Parameter	Least Squares Means		Observed Difference (%) [1]	Power	90% Confidence Interval [2]	
	Test	Reference			Lower (%)	Upper (%)
AUC 0-t (ng-hr/ml)	363.9	383.0	-5.01	0.61	-19.6	9.6
AUCinf (ng-hr/ml)	395.1	445.6	-11.34	0.53	-27.5	4.8
Cmax (ng/ml)	67.90	68.31	-0.60	0.78	-12.7	11.5
Tmax (hour)	2.08	2.20	-5.52	0.98	-	-
Ke (1/hour)	0.1597	0.1585	0.79	0.72	-	-
Elimhalf (hour)	6.17	6.38	-3.37	0.60	-	-

[1] Observed difference calculated as: [(Test - Reference) / Reference] x 100. None of the differences were detected as statistically significant by ANOVA ($\alpha = 0.05$).
[2] Confidence interval on the observed difference.

Table 1.4: Ln-transformation of the propoxyphene pharmacokinetic data, including data from Subject 08.

Parameter	Geometric Mean Ratio: Test/Reference	90% Confidence Interval on Ratio	
		Lower	Upper
AUC 0-t	0.955	0.830	1.098
AUCinf	0.916	0.790	1.062
Cmax	0.983	0.873	1.107

Table 1.5. Summary of propoxyphene statistical comparisons at each sampling time comparing Vintage's 100 mg propoxyphene napsylate and 650 mg acetaminophen combination tablets (Test) vs. Darvocet-N® 100 tablets (Reference) when given as a single fasted dose to 31 subjects.

Collection (Hour)	Least Squares Means (ng/ml)		Significance
	Test	Reference	
Pre-dose	0.00	0.00	-
0.25	0.00	0.00	-
0.5	6.49	2.10	N.S.
1.0	42.34	34.29	N.S.
1.5	57.10	57.06	N.S.
2.0	60.02	63.52	N.S.
2.5	57.30	61.96	N.S.
3.0	53.00	56.68	N.S.
4.0	41.67	43.77	N.S.
6.0	23.36	24.42	N.S.
8.0	15.93	16.48	N.S.
12.0	7.26	7.75	N.S.
16.0	4.44	5.18	N.S.
24.0	1.71	2.16	N.S.
30.0	1.17	1.50	N.S.

N.S. = not significant ($p = >0.05$)

Table 2.1 summarizes the results of the acetaminophen statistical analyses of the major bioavailability parameters. Natural log-transformation of the area and Cmax parameters was also performed and analyzed statistically (Tables 2.2). Statistical comparisons of the test and reference formulations at each sampling time are summarized in Tables 2.3.

The plasma concentration-time mean profiles (N=31) for the test and reference products are similar to each other (Table 2.3 and Figure 2).

Table 2.1. Comparisons of acetaminophen results for Vintage's 100 mg propoxyphene napsylate/650 mg acetaminophen tablets (Test) vs. Darvocet-N^R 100 tablets (Reference) when given as a single fasted dose to 31 subjects.

Parameter	Least Squares Means		Observed Difference (%) [1]	Power	90% Confidence Interval [2]	
	Test	Reference			Lower (%)	Upper (%)
AUC 0-t (μg-hr/ml)	28.23	27.65	2.12	>0.99	-0.9	5.1
AUCinf (μg-hr/ml)	29.30	28.21	3.85	>0.99	0.3	7.5
Cmax (μg/ml)	7.929	7.767	2.10	0.98	-6.1	10.3
Tmax (hour)	0.96	0.98	-2.59	0.37	-	-
Ke (1/hour)	0.1838	0.1939	-5.21	>0.99	-	-
Elimhalf (hour)	4.07	3.80	7.10	>0.99	-	-

[1] Observed difference calculated as: [(Test - Reference) / Reference] x 100. None of the differences were detected as statistically significant by ANOVA ($\alpha = 0.05$).

[2] Confidence interval on the observed difference.

Table 2.2. Ln-transformation of the acetaminophen pharmacokinetic data (n=31).

Parameter	Geometric Mean Ratio: Test/Reference	90% Confidence Interval on Ratio	
		Lower	Upper
AUC 0-t	1.020	0.992	1.049
AUCinf	1.035	1.002	1.068
Cmax	1.004	0.925	1.090

Table 2.3. Summary of acetaminophen statistical comparisons at each sampling time comparing Vintage's 100 mg propoxyphene napsylate and 650 mg acetaminophen combination tablets (Test) vs. Darvocet-N[R] 100 tablets (Reference) when given as a single fasted dose to 31 subjects.

Collection (Hour)	Least Squares Means (µg/ml)		Significance
	Test	Reference	
Pre-dose	0.004	0.000	N.S.
0.25	1.887	0.769	N.S.
0.5	6.081	5.252	N.S.
1.0	6.324	6.785	N.S.
1.5	5.735	5.992	N.S.
2.0	5.149	5.109	N.S.
2.5	4.387	4.318	N.S.
3.0	3.775	3.673	N.S.
4.0	2.707	2.646	N.S.
6.0	1.475	1.429	N.S.
8.0	0.850	0.843	N.S.
12.0	0.384	0.382	N.S.
16.0	0.196	0.190	N.S.
24.0	0.030	0.029	N.S.
30.0	0.004	0.004	N.S.

N.S. = not significant (p = >0.05)

Approximately 7.2% of the study propoxyphene samples were reanalyzed when compared to the total number of study samples. Approximately 1.18% of the acetaminophen study samples were reanalyzed when compared to the total number of study samples.

The subjects were monitored throughout the study for any adverse experiences. They were encouraged to report signs, symptoms, and any changes in health to the study nurse. Severity of each adverse event was determined by the study nurse based on observation and questioning of the subject. The Investigator judged the relationship of the event to the study treatments. None of the adverse events experienced by the subjects during this study was judged as serious.

Comparative dissolution was conducted by the firm on its Propoxyphene Napsylate/Acetaminophen Tablet, 100 mg/650 mg, lot #031054 and Davocet-N 100. The method and results are presented in Table 3. The content uniformity ranges were 100.2-114.8%/98.2-110.0% (CV=4.7/3.9%) for the test product. The composition of the test product is shown in Table 4.

XI. Comments

1. When the propoxyphene elimination data were examined, it was apparent that the difference in elimination halflives for Subject 08 between Periods I (after the reference) and Period II (after the test) was dramatically different (halflives were 13.8 and 3.9 hours, respectively). No other subject demonstrated such a difference between study periods. The elimination phase for Subject 08 may not have been adequately characterized for Period II because the concentration of propoxyphene after 12 hours fell below the level of sensitivity for the assay. Due to an inadequate characterization of the propoxyphene elimination rate constant for Subject 08, statistical analyses of the propoxyphene elimination parameters and area to infinity were performed without this subject's data which resulted in the $AUC_{0\text{-}inf}$ falling within the limits of 80% to 125%. For completeness, these analyses were also presented with this subject's data included which resulted in 79% as the lower limit of the 90% confidence interval for $AUC_{0\text{-}inf}$ for propoxyphene.

2. Based on meeting 90% confidence interval criteria for AUC and peak concentrations C_{max} using log-transformed data Vintage's generic test tablets were shown to be bioequivalent to the reference Darvocet-N^{R} 100 tablets with respect to propoxyphene and acetaminophen.

3. Individual test/reference ratios of the pharmacokinetic parameters $AUC_{0\text{-}t}$ and C_{max} for propoxyphene napsylate and acetaminophen are shown in Tables 5 and 6, respectivelly. This data is included for potential future use and is not used in evaluating the current application.

4. Individual test and reference $AUC_{0\text{-}t}/AUC_{0\text{-}inf}$ ratios for propoxyphene and acetaminophen are shown in Tables 7 and 8, respectivelly. This data is not used in evaluating the current application.

5. The reported confidence intervals for $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, C_{max}, and the reported test/reference geometric mean ratios are in agreement with the calculations of the reviewer.

6. Calculations of $AUC_{0\text{-}t}$ were done by the reviewer and the results agree with the firm's calculations.

XII. Recommendations

1. The bioequivalence study conducted by Vintage Pharmaceuticals, Inc. on its Propoxyphene Napsylate/Acetaminophen tablet, 100 mg/650 mg, Lot # 031054, comparing to Davocet-N 100, is acceptable by the Division of Bioequivalence. The study demonstrates that Vintage Pharmaceuticals' Propoxyphene Napsylate/Acetaminophen tablet, 100 mg/650 mg, is bioequivalent to the reference products, Davocet-N 100, manufactured by Eli Lilly Company.

2. The dissolution testing data presented by Vintage Pharmaceuticals, Inc. on its Propoxyphene Napsylate/Acetaminophen tablet, 100 mg/650 mg, Lot # 031054, comparing to Davocet-N 100, is acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of pH 4.5 acetate buffer, at 37° using USP XXIII apparatus I (basket) at 100 rpm. The test product should meet the following specifications:

   Not less than of the labeled amount of both propoxyphene napsylate and acetaminophen in the dosage form are dissolved in 60 minutes.

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang _____
FT INITIALED YCHuang _____

Conc _____ Date: 7/10/96

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence

cc: ANDA 74-843 (original), HFD-600 (Hare), HFD-630, HFD-344 (Viswanathan), HFD-652 (Huang, Chaney), Drug File, Division File

JEC/070996/WP#74843S.196

Table 3. In Vitro Dissolution Testing

Drug (Generic Name): Propoxyphene Napsylate /Acetaminophen
Dose Strength: 100 mg/650 mg tablet
ANDA No.: 74-843
Firm: Vintage Pharmaceuticals, Inc.
Submission Date: January 31, 1996
File Name: 74843S.196

I. Conditions for Dissolution Testing:

USP XXIII Basket: X Paddle: RPM: 100No. Units Tested: 12
Medium: Sodium Acetate Buffer pH 4.5; Volume: 500 ml
Specifications: NLT (Q) of labelled amount in 60 minutes (both active components)
Reference Drug: DARVOCET - N100
Assay Methodology

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 031054 Strength(mg) 650			Reference Product Lot # 9AC14A Strength(mg) 650		
	Acetaminophen					
	Mean %	Range	%CV	Mean %	Range	%CV
10	82.8		12.9	59.4		19.2
20	102.1		3.4	95.3		6.6
30	103.0		8.9	100.6		3.4
45	105.7		4.2	101.7		5.3
60	106.3		2.9	100.9		2.8
	Propoxyphene Napsylate					
	Mean %	Range	%CV	Mean %	Range	%CV
10	61.7		14.9	36.0		17.8
20	88.1		4.0	73.8		6.4
30	97.1		4.9	88.8		4.6
45	99.4		4.0	94.9		6.5
60	100.7		4.3	96.2		5.1

Table 4. Composition of Vintage Pharmaceuticals' Propoxyphene Napsylate/Acetaminophen Tablets, USP 100 mg/650 mg

Ingredients:	Contents (mg/tablet)	
Core		
Acetaminophen USP, Powder	650.0	
Propoxyphene Napsylate, USP	100.0	
Hydroxypropyl Methylcellulose, USP		
Sodium Starch Glycolate, NF		
Lactose Monohydrate, NF		
Magnesium Stearate, NF		
Deionized Water		
Total	910.00	1010.10
Coating		

Table 5. Individual Test/Reference Ratios for Pharmacokinetic Parameters (AUC_{0-t}, AUC_{0-inf} and C_{max}) of **Propoxyphene** Following Oral Dosing of Propoxyphene Napsylate/Acetaminophen tablet, 100 mg/650 mg and Reference Davocet-N 100, manufactured by Eli Lilly Company.

SUBJ	AUC_{0-t}	AUC_{0-inf}	C_{max}
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			
27			
28			
29			
30			
31			

Table 6. Individual Test/Reference Ratios for Pharmacokinetic Parameters (AUC_{0-t}, AUC_{0-inf} and C_{max}) of **Acetaminophen** Following Oral Dosing of Propoxyphene Napsylate/Acetaminophen Tablet, 100 mg/650 mg and Reference Davocet-N 100, manufactured by Eli Lilly Company.

SUBJ	AUC_{0-t}	AUC_{0-inf}	C_{max}
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			
27			
28			
29			
30			
31			

Table 7. Individual Test and Reference AUC_{0-t}/AUC_{0-inf} Ratios For **Propoxyphene** Following Oral Dosing of Propoxyphene Napsylate/Acetaminophen tablet, 100 mg/650 mg and Reference Davocet-N 100, Manufactured by Eli Lilly Company.

Subject	Test	Ref
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		
16		
17		
18		
19		
20		
21		
22		
23		
24		
25		
26		
27		
28		
29		
30		
31		

Table 8. Individual Test and Reference AUC_{0-t}/AUC_{0-inf} Ratios For **Acetamnophen** Following Oral Dosing of Propoxyphene Napsylate/Acetaminophen tablet. 100 mg/650 mg and Reference Davocet-N 100, manufactured by Eli Lilly Company.

Subject	Test	Reference
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		
16		
17		
18		
19		
20		
21		
22		
23		
24		
25		
26		
27		
28		
29		
30		
31		

FIGURE 1

STUDY NO. 9528050B

LEAST-SQUARES MEAN PROPOXYPHENE PLASMA CONCENTRATIONS (N=31)

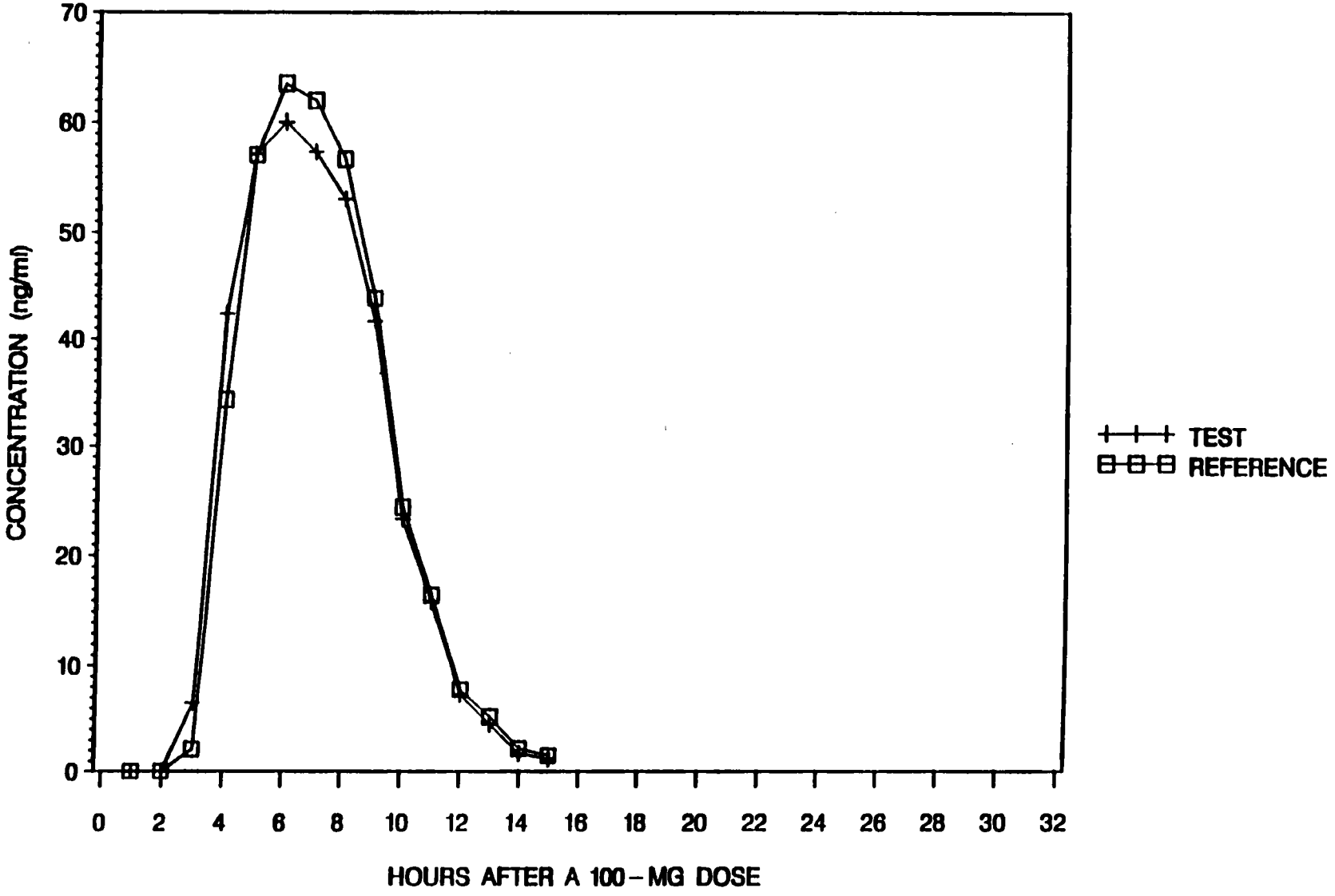
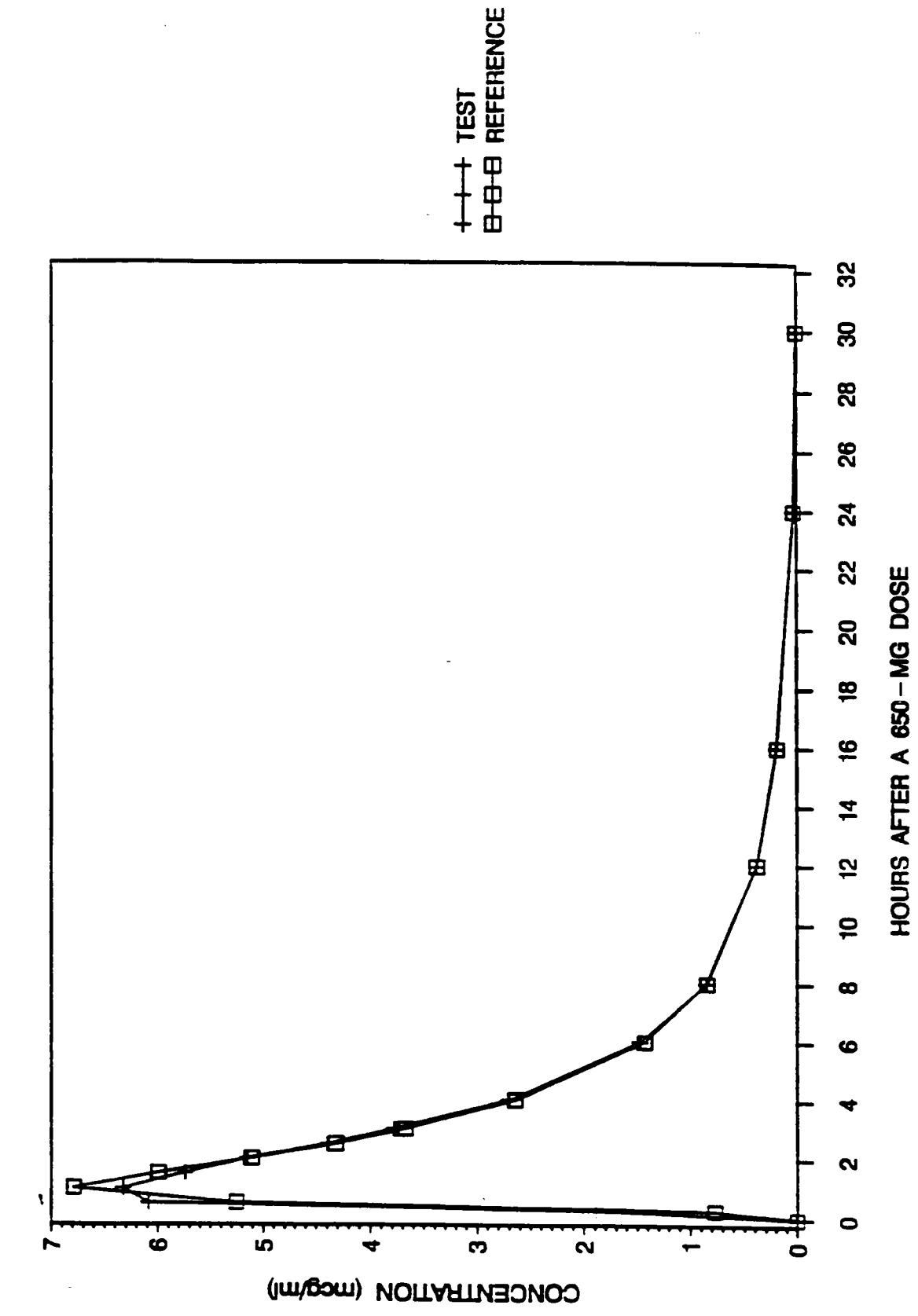


FIGURE 2


STUDY NO. 9528050B
LEAST-SQUARES MEAN ACETAMINOPHEN PLASMA CONCENTRATIONS (N=31)
TEST
REFERENCE
CONCENTRATION (mcg/ml)
0
1
2
3
4
5
6
7
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
HOURS AFTER A 650-MG DOSE

FEB 4 1997

Propoxyphene Napsylate/
Acetaminophen
Tablet, 100 mg/ 650 mg
ANDA #74-843
Reviewer: James Chaney
WP#74843A.196

Vintage Pharmaceuticals, Inc.
Charlotte, North Carolina
Submission Date:
January 31, 1996
March 5, 1996
May 30, 1996
June 5, 1996

An Amendment To The 07/10/96 Review of a Bioequivalence Study

The firm used only 22 of the 31 subjects who finished the bioequivalence study in its statistical analysis of AUCo-inf, Ke and halflife. The 90% confidence interval for the propoxyphene $AUC_{0\text{-}inf}$ parameter was marginal (79.0-106.2). It appeared to the reviewer that not all of the nine subjects did not need to be deleted, although the firm did not pesent any criteria for selecting terminal data. Therefore the reviewer included six additional subjects and used them in the statistical analysis. The result was that the confidence interval range actually improved (see Table 1).

Table 1. Comparisons of propoxyphene statistical results for Vintage's 100 mg propoxyphene napsylate and 650 mg acetaminophen combination tablets (Test) vs. Darvocet-N^R 100 tablets (Reference) when given as a single fasted dose to 31 subjects. The AUCo-inf results were obtained including 22 and 28 subjects in the statistical analysis.

Parameter	N	LS Means Test	LS Means Reference	T/R	Confidence Intervals
AUCo-inf	22*	395.1	445.6	0.89	79.0-106.2
AUCo-inf	28**	348.0	362.9	0.96	82.3-111.7

* The 22 subjects were #'s 1, 2, 3, 6, 7, 8, 11, 12, 13, 14, 16, 18, 19, 20, 21, 22, 23, 24, 28, 29, 30 and 31.

** The 28 subjects were #'s 1, 2, 3, 4. 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 19, 20, 21, 22, 23, 24, 25, 26, 28, 29, 30 and 31.

The above subjects in Table 1 include subject 8. The firm originally eliminated subject 8 resulting in a confidence interval of 87.4-110 for propoxyphene. The firm pointed out that the difference in elimination halflives for Subject 08 between Periods I (after the reference) and Period II (after the test) was dramatically different (halflives were 13.8 and 3.9 hours, respectively). The firm suggested that the elimination phase for Subject 08 may not have been adequately characterized for Period II because the concentration of propoxyphene after 12 hours fell below the level of sensitivity for the assay. In retrospect the reviewer has determined that this might not be sufficient reason to eliminate the subject.

Also, it was discovered that the plasma concentration-time mean profile for propoxyphene was wrong. Attached is the correct profile generated from SAS analysis by the reviewer. See Figure 1 for the new profile. The correct plasma concentration-time mean profiles (N=31) for the test and reference products are similar to each other (Figure 1).

Comment

Based on meeting the 90% confidence interval criteria for AUC_{0-t}, AUC_{0-inf} and C_{max} using log-transformed data and the Test/Reference ratio requirements for these pharmacokinetic parameters Vintage's generic test tablets are bioequivalent to the reference Darvocet-N^R 100 tablets with respect to propoxyphene and acetaminophen.

Recommendations

1. The bioequivalence study conducted by Vintage Pharmaceuticals, Inc. on its Propoxyphene Napsylate/Acetaminophen tablet, 100 mg/650 mg, Lot # 031054, comparing it to Davocet-N 100, is acceptable by the Division of Bioequivalence. The study demonstrates that Vintage Pharmaceuticals' Propoxyphene Napsylate/Acetaminophen tablet, 100 mg/650 mg, is bioequivalent to the reference product, Davocet-N 100, manufactured by Eli Lilly Company.

2. No further action is required on this application and it is approvable.

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang _____
FT INITIALED YCHuang _____ 2/4/97

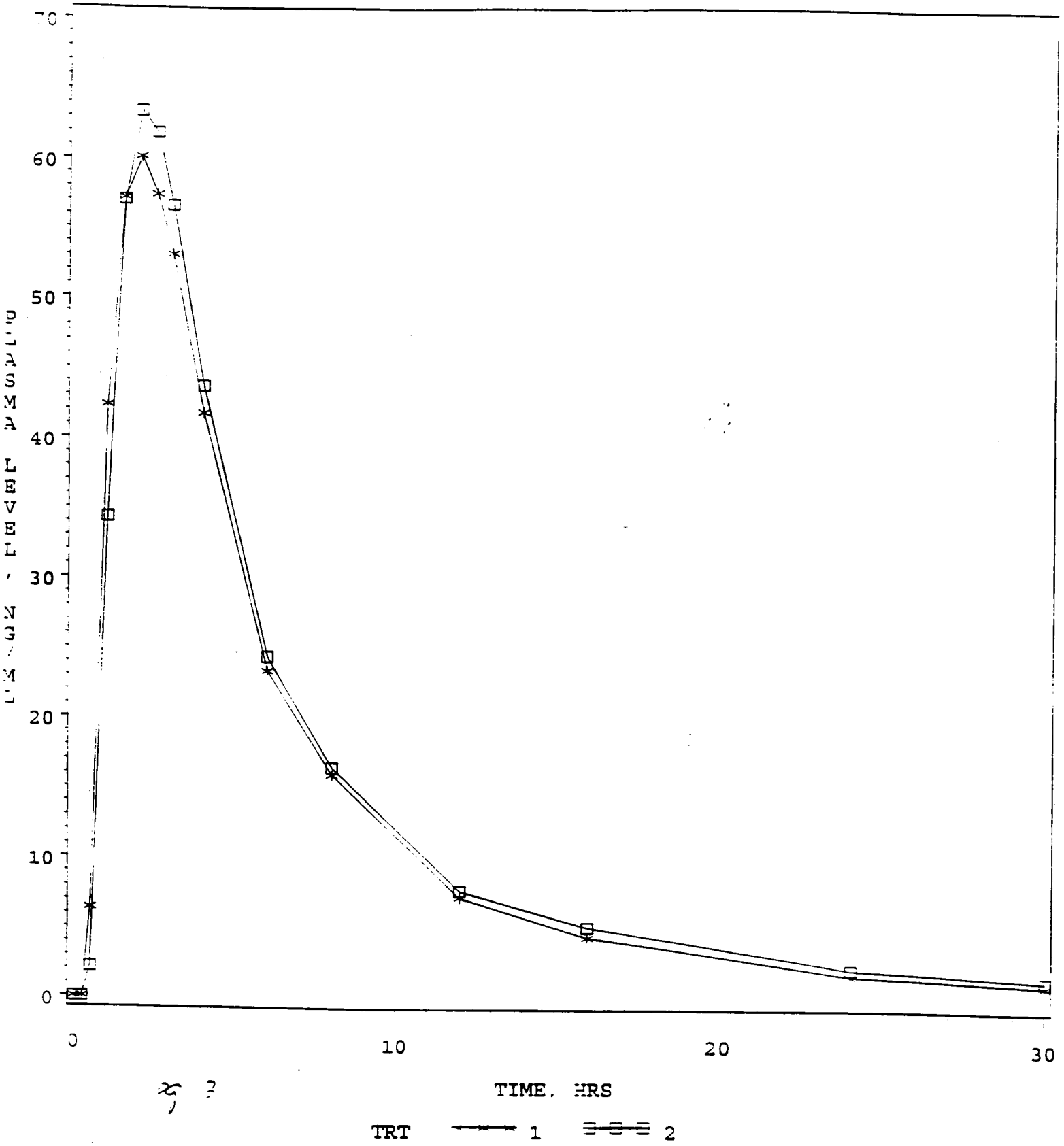
Concur: _____ Date: 2/4/97
Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence

cc: ANDA 74-843 (original), Chaney, HFD-652, (Huang,), Drug File, Division File

JEC/020397/WP#74843A.196

FIG 1. PLASMA PROpoxypheNE LEVELS

74-843



1=TEST PRODUCT(VINTAGE) 2=REFERENCE PRODUCT(LILLY)